GIENS WORKSHOPS 2018/ORGANIZATIONAL AND REGULATORY ASPECTS

Early access to health products in France: Major advances of the French ‘‘Conseil stratégique des industries de santé’’ (CSIS) to be implemented (modalities, regulations, funding)☆

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Summary  In a context of perpetual evolution of treatments, access to therapeutic innovation is a major challenge for patients and the various players involved in the procedures of access to medicines. The revolutions in genomic and personalized medicine, artificial intelligence and biotechnology will transform the medicine of tomorrow and the organization of our health system. It is therefore fundamental that France prepares for these changes and supports the development of its companies in these new areas. The recent "Conseil stratégique des industries de santé" launched by Matignon makes it possible to propose a regulatory arsenal conducive to the implementation and diffusion of therapeutic innovations. In this workshop, we present a number of proposals, our approach having remained pragmatic with a permanent concern to be effective in the short term for the patients and to simplify the procedures as much as possible. This was achieved thanks to the participation in this workshop of most of the players involved (industrial companies, "Agence nationale de sécurité du médicament et des produits de santé", "Haute Autorité de santé", "Institut national du cancer", "Les entreprises du médicament", hospitals, "Observatoire du médicament, des dispositifs médicaux et de l'innovation thérapeutique"...). The main proposals tend to favor the implementation of clinical trials on our territory, especially the early phases, a wider access to innovations by favoring early access programs and setting up a process called "autorisation temporaire d'utilisation d'extension" (ATUext) that make it possible to prescribe a medicinal product even if the latter has a marketing authorisation in another indication. In addition, we propose a conditional reimbursement that will be available based on preliminary data but will require re-evaluation based on consolidated data from clinical trials and/or real-life data. Finally, in order to better carry out these assessments, with a view to access or care, we propose the establishment of partnership agreements with health agencies/hospitals in order to encourage the emergence of field experts, in order to prioritize an ascending expertise closer to patients' needs and to real life.

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Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
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<tr>
<td>AB</td>
<td>actual benefit</td>
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<tr>
<td>ANSM</td>
<td>Agence nationale de sécurité du médicament et des produits de santé (French national agency for medicines and health products safety)</td>
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<tr>
<td>ATU</td>
<td>autorisation temporaire d'utilisation (temporary authorisation for use)</td>
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<tr>
<td>ATUc</td>
<td>autorisation temporaire d'utilisation de cohorte (cohort temporary authorisation for use)</td>
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<td>ATUex</td>
<td>autorisation temporaire d'utilisation d'extension (extension temporary authorisation for use)</td>
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<tr>
<td>ATUn</td>
<td>autorisation temporaire d'utilisation nominative (nominative temporary authorisation for use)</td>
</tr>
<tr>
<td>B/R</td>
<td>benefit/risk</td>
</tr>
<tr>
<td>CEESP</td>
<td>Commission d'évaluation économique et de santé publique (Economic and public health assessment committee)</td>
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<tr>
<td>CEPS</td>
<td>Comité économique des produits de santé (Economic committee for health products)</td>
</tr>
<tr>
<td>CHG</td>
<td>centre hospitalier général (general hospital centre)</td>
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</table>
Introduction — Early access challenges

Given the acceleration of the development of new medicinal products for serious clinical situations where the medical need is unmet or poorly covered and promising initial results in immunotherapy, targeted therapies and CAR-T cell therapy\(^1\) in haematology-oncology, the possibility of early access to these therapies pending more in-depth assessments for marketing authorisation (MA) and reimbursement is becoming an increasingly important issue. According to the Haute Autorité de santé (HAS) or the French national authority for health, a new medicinal product can be considered an innovation when it saves or changes the lives of patients with a serious or evolving disease in the context of an unmet or poorly covered medical need (no alternative or inappropriate alternatives) [1]. It is therefore essential that medicinal products be made available rapidly when the therapeutic progress deriving from the innovation is significant for the management of patients with a disease qualified as serious (that is, to say with a life-threatening impact like for example cancer), for which the medical need remains unmet or poorly covered and there is no real therapeutic alternative, and which is presumed to have an impact on morbidity and mortality based on preliminary data.

This involves four challenges.

- The first challenge is related to the time required for a medicinal product to be made available through a clinical trial, a temporary authorisation for use (ATU), a MA and reimbursement by social security. Thus, the criteria for early access to innovation must be viewed differently (positive benefit/risk \([B/R]\) ratio, relative \(B/R\) ratio) depending on whether one is considering:
  - provision of the medicinal product which depends on the presumption that the \(B/R\) ratio is positive,
  - or reimbursement which depends on the product’s \(B/R\) ratio relative to a comparator.

Because of a clear and understandable wish to make something that can be considered as a possible innovation available at an early stage, the assessment criteria used may be insufficiently robust, requiring the implementation of specific regulatory mechanisms suited to the management of uncertainties (conditional marketing authorisation, temporary reimbursement).

Although France is the only country with a single procedure for early access outside a clinical trial and before MA, the ATU, the period between the MA and the publication in the official journal (JO) of the price of the medicinal product is nonetheless significant [2]. Although the current process is well managed, it is lengthy because of a succession of procedures that follow each other from the MA until the publication of the price and reimbursement conditions in the JO.

In terms of reimbursement, in France, the transparency committee (TC) of the HAS independently assesses the actual benefit (AB) and the improvement in actual benefit (IAB) of new medicinal products in view of their potential reimbursement by social security, and if a significant medical-economic impact is expected, a corresponding assessment is conducted by the economic and public health assessment committee (CEESP) of the HAS.

Price negotiations are then undertaken on the basis of these assessments by the Economic committee for health products (CEPS) and the industrialists. The whole process, including the qualitative and economic assessment, the negotiations and publication of the price in the JO, takes an average of 530 days in France [3]. This average period is much longer than the average periods observed in comparable countries and far longer than the deadline set by the European commission in 1989 (180 days) [4]. The price negotiations between the industrialists and the CEPS take the most time (2/3 of the time). Therefore, if a health product is assumed to represent a major progress, it is normal that patients should be able to benefit from the possible therapeutic advance more quickly to avoid any loss of opportunity, and all the more so if the indication is for a therapeutic need that is as yet unmet.

\(^1\) Treatment with CAR-T cells consists in taking T cells from the patient, genetically reprogramming them to recognize and attack the tumors, then culturing them and re-injecting them into the patient.
The second challenge is related to the way how early the product is made available given that the treatment is still under development. Managing the risk and/or clinical benefit for the patient and the financial aspects for the community is a major issue; early access can only be granted if the monitoring and re-assessment processes are reinforced and it may be contingent on the generation of additional data and appropriate pricing and conditional reimbursement dependant on the presentation of new confirmatory data.

The third challenge concerns the capacity to guarantee continued access to the medicinal product, implying that each step feeds the next in terms of data generation, in order to avoid treatment and knowledge collapses.

The last challenge relates to the reversibility of the decision and the absolute necessity of re-assessing the latest data in order to make consolidated decisions. In addition, it may be risky for a patient to have early access to a medicinal product given the preliminary nature of the data and the lack of clear or consolidated visibility regarding the benefit/risk analysis (for example, a response that may be considered a benefit may not necessarily be an advantage in terms of survival that can only be measured by analysis of data obtained at a later stage, or the lack of hindsight on an innovative product may expose patients to a risk of side effects that weren’t considered initially but may be revealed through the pharmacovigilance process).

In this paper, we address two major aspects of the early access process: the provision of medicinal products (ATU, temporary use recommendation [RTU] and MA) and their financing (reimbursement/price). For each point, we provide a description of the current situation as well as the problems encountered, and we give practical recommendations that can be implemented in the short and medium term.

The early access theme, selected during this working session at the Giens 2018 workshops, echoes a new impetus given by our government, illustrated by the 2018 proposals of the Strategic council for health industries (CSIS) issued in July 2018 aiming to promote the integration and development of a coordinated strategy that facilitates patient access to what is presumed to be a therapeutic innovation [5,6].

The possible ways of gaining early access to innovative therapies

Clinical trials

Clinical trials are chronologically the first opportunity for early access to treatment in serious diseases, especially when the medical need is insufficiently met for the patient. They are also an opportunity for practitioners to experiment the use of a medicinal product under development. The implementation stage of clinical trials is also a perfect time to observe patient treatment pathways, to optimize them and better appreciate the technicalities of the care required by the patients.

It is a major strategic challenge for France to remain attractive in this area so it may contribute actively to the development of medicinal products, which has become global and is subject to competition, so patients and practitioners can benefit from these opportunities [7,8]. Moreover, the initiation of early phase clinical trials (I and I/II) in France can be an asset in the further development of a molecule and ultimately, when the choice of the rapporteur country or countries is made during the European medicines agency’s (EMA) assessment of the B/R ratio for a marketing authorisation. The forthcoming implementation of a European regulation on clinical trials on medicinal products for human use (Regulation [EU] No. 536/2014 of the European parliament and of the Council of 16 April 2014 on clinical trials of medicinal products for human use and repealing Directive 2001/20/EC, text with EEA relevance), which will be applicable at the end of 2020 also requires our country to better organize itself so it may become a privileged and facilitating country in the context of Member State clinical trial mutual assessments [9]. The regulation introduces a new authorisation procedure including:

- two assessment phases of the scientific aspects (part 1): coordinated assessment of all concerned Member States and ethical committees (part 2): assessment by each Member State;
- a final national authorisation decision, unique to each Member State, incorporating the conclusions of the assessment of parts 1 and 2.

Should a Member-State (MS) disagree with the conclusion of the rapporteur Member-State (RMS), the MS may withdraw from the procedure in the event of:

- significant differences in ”normal clinical practice” which may result in lower quality treatment for the patient in the relevant MS;
- violation of national legislation (Article 86: medicinal product containing cells);
- a disagreement with the conclusion of the RMS on patient safety, quality and robustness (consistency) of the submitted data.

It should be noted that beyond the technical capabilities of the investigating centres and their capacity to include patients, the concept of speed in setting up a clinical trial is critical. Before a contract can be drawn up with investigating centres, the setting up of a clinical trial requires the issuing of a scientific authorisation by the French national agency for medicines and health products safety (ANSM) and a positive opinion by an ethics committee (EC). While double scientific and ethical validation is required to guarantee the quality and safety of medical research on humans, the two procedures should take place simultaneously to minimize administrative delays to the granting of the authorisation.

Thus, the ANSM must assess trials with a view to authorising them within a limited timeframe while at the same time playing its protective role with regards to patients. In the interest of patients, the Agency must ensure that all clinical trials will be conducted under conditions of optimal safety and that patients will not lose an opportunity by participating in a trial that does not conform to therapeutic recommendations; however it must also preserve the opportunity for patients to participate in a clinical trial that could represent a chance for them.

The ANSM assessment must be carried out in parallel with the ethics committee assessment so not to delay the
assessment process. The law relating to ethics committees, which was promulgated on October 18, 2018 in the official journal [10] and which concerns the random designation of only the available committees which are competent in the field, should be a lever to reduce currently observed ethics committee delays.

In 2017, the ANSM issued 727 clinical trial authorisations for medicinal products and 2682 amendments or substantial amendments. Although France is historically a country that contributes strongly to clinical development, the total number of clinical trials conducted in France in 2016 and 2017 calls for vigilance (Table 1) [11].

The concept of a period of authorisation and therefore of implementation is critical. Wishing to be more responsive and in line with the needs of the field [12], the ANSM has already implemented several measures. As of June 2017, a task force within the ANSM’s department of haematology-oncology, a field representing 50% of all the clinical trials conducted in France, started working on the better management of deadlines and developed a new two-part assessment paradigm at the root of a new assessment strategy. The first part consisted in designing an optimized prioritization tool based on the type of the trial founded on an analysis of risks and determination of a criticality scale (Appendix 1). This scale is based on 4 dimensions that depend on the study design, the target population and the treatment under study:
• C1: lack of hindsight on the safety of the study treatment;
• C2: high exposure of a population (trials conducted exclusively in France, paediatric population);
• C3: risk of a loss of opportunity (many therapeutic alternatives, not much data on the study treatment);
• C4: type of dossier (genome-guided trials, trials with multiple experimental arms).

Each dimension gives a binary score (no = 0, yes = 1). The addition of these four scores gives a total criticality score of 0 to 4 which then determines the type of assessment to be adopted for the trial in question. High-criticality trials are subjected to an in-depth assessment while low-criticality trials are subjected to a more targeted assessment focusing on specific problems (treatment safety, loss of opportunity, etc.).

The second part consisted in implementing a multidisciplinary cooperative decision-making process at the different stages of the assessment. This assessment method was developed in collaboration with the groupe hospitalier mutualiste de Grenoble which offered smooth and effortless access to “in situ” expertise in phase with the needs and reality of patient care.

A pre-submission and “early advice” principle allowing sponsors to come present their trials and, if required, be given the ANSM’s first comments, was also put implemented for trials with a complex design. The trials concerned by this principle include genome-guided trials (precision medicine) [13,14] and adaptive trials which, according to different methods, formulate hypotheses during the trials in the light of advances in participant outcomes unlike “classical” experimental trials that require the formulation beforehand of a series of hypotheses on the properties of the treatment requiring testing.

In terms of authorisation delays, very significant progress has already been made, with the average decision time having dropped from more than 100 days before June 2017 to 45 days in 2018, leading to decisions being issued within regulatory deadlines in 90% of cases.

To allow ever faster access to innovative treatments for patients, the ANSM has set up two short circuit procedures (fast track procedures) which will help reduce authorisation application processing times for clinical trials on medicinal products without neglecting patient safety. This new approach launched on October 15, 2018, concerns clinical trials on innovative treatments and new trials with known molecules. Depending on the type of trial, applications will be processed within 40 or 25 days at the most instead of the current regulatory 60 days [15]:

- fast track procedure 1 promotes access to innovation: it concerns early trials (phase I), tests in paediatric oncology and haematology, rare diseases, and support for innovation (hospital clinical research program [PHRC], INCa-certified centre for early phase studies [CLIP²]) with a target approval period of 40 days at the most;
- fast track procedure 2 supports development: its purpose is to accelerate the setting up of clinical trials for molecules or combinations of molecules already assessed by the ANSM with a target approval period of 25 days at the most.

In addition, the setting up of a cell for early trials in December 2017 within the former assessment department, newly named the authorisation and innovation policies division (DPAI), has made it possible to centralize the assessment of phase I clinical trials and optimize the management of safety signals.

As regards clinical trials, following the review, the round table focused on two key themes: the conditions in which France may pioneer early access via clinical trials and how to make regulatory approvals more fluid so that industrialists opt for our model for the assessment of their molecules. Currently France’s position in clinical trials is not very prominent [16] although, according to the latest report of the LEEM (Les entreprises du medicament [French industry association representing drug companies operating in France]) issued in 2016, it continues to be among the major players

Table 1 Review of clinical trial authorisation dossiers submitted in France between 2013 and 2017 [11].

<table>
<thead>
<tr>
<th>Medicinal product clinical trials authorisations</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Authorisations delivered (initial requests)</td>
<td>899</td>
<td>821</td>
<td>928</td>
<td>756</td>
<td>727</td>
</tr>
<tr>
<td>Authorisations delivered (application for substantial amendments)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>2,682</td>
</tr>
</tbody>
</table>

Courtesy Agence nationale de sécurité du médicament et des produits de santé (ANSM).
in global clinical research with 10% of international studies carried out in France. French patients represent 8.8% of the total number of patients included in international studies in 2016, compared to 5.9% in 2014 [17].

Although the ANSM has implemented FT procedures, the gains achieved in terms of delays could be neutralized by ethics committee delays which also contribute to lengthening the authorisation procedures preceding clinical trials.

Proposal 1: In parallel to the ANSM’s fast track procedure, implement ethics committee Fast Track procedures allowing the investigator/sponsor to interact directly with the ethics committee. While respecting the independence of the ethics committee/ANSM, set up collective exchange times during trial assessments as the problem of the loss of opportunity is often common to both assessments, the aim being for ethics committees to issue opinions in the same timeframes as the ANSM. Pharmaceutical professionals must commit to launching the early phase trials as soon as possible.

Proposal 2: Create a favourable ecosystem, similar to that set up by the INCa (CLIP²) for the implementation of Phase I trials, capitalizing on the experience gained in oncology and particularly in the coordination of Laboratory/biomarker platforms, expert centres/university hospital centres (CHU)/general hospital centres (CHG).

Proposal 3: Engage institutional players at an early stage in a methodological reflection taking into account the prerequisites for obtaining a MA, but also for reimbursement and later financing (concept of continuum) through academic/institutional/industrial consortiums. Favour contact between decision-makers and sponsors at the time of clinical development and clinical trials using the “scientific advice” and “early dialogue” models.

What methodologies should be implemented to allow early access and that will give predictable and homogeneous results in different therapeutic areas? There are indeed problems related to uncertainties about the specifications allowing early access and financing. Key questions to consider include: the population to be included, comparators, assessment criteria, study design, number of patients, discontinuation criteria, place in the therapeutic strategy and amount of effect.

A persistent problem is that of the methodology to be adopted in the case of small numbers of patients and the difficulty of validating a benefit observed in a non-comparative situation by a comparative phase III trial. From the point of view of HAS, a direct comparative study should be conducted as soon as it is possible. Phase III studies on small numbers of patients are performed regularly and assessed by the TC (for targeted or stratified therapies [19], ALK- lung cancer, rare diseases). While a comparison is expected, the comparison methodology may be discussed depending on the context (direct comparison, indirect comparisons using individual data, comparison with a historical cohort). The trial model of the AcSe (secure access to innovative targeted therapies) programme coordinated by the INCa can contribute to an assessment without substituting a comparative phase III trial. The AcSe programme, launched in 2013 by the INCa with the agreement of the ANSM, aims to promote innovation in the interest of patients by offering secure access to targeted therapies that already have a cancer treatment indication by participation in exploratory early phase clinical trials, so as to avoid off-label use or the repetitive use of nominative ATUs, which are unsafe for patients and do not allow optimal data collection. Equity of access on the national territory is a major objective with extensive opening of centres (about 250 French institutions offer these trials), but without competing with development trials which remain a priority. The programme allows patients whose treatment has failed to integrate phase II trials in which they have access to innovative therapies as a function of the molecular features of their tumours. This programme has thus allowed access to innovation in a cohort with a limited number of patients, the setting up of a relay by the implementation of a temporary use recommendation for crizotinib, a MA and finally a reimbursement proposal by the HAS (low actual benefit given the preliminary nature of the data).
Early access to health products in France

Proposal 4: Encourage the setting up of future trials allowing early access, like the AcSé-pilot programme (INCa).

Temporary authorisation for use (ATU)

There is a process specific to France that can be implemented by derogation and exceptionally, which allows early access to medicinal products outside clinical trials and prior to MA and which is referred to as a temporary authorisation for use (ATU) [20]. This process allows much faster access to medicinal products upstream of the MA.

Temporary authorisations for use are issued by the ANSM under three conditions as follows:

- the medicinal products are intended to treat, prevent or diagnose serious or rare diseases;
- there is no appropriate treatment available on the market;
- the efficacy and safety of the medicinal products are presumed to be favourable based on current scientific knowledge and implementation of treatment cannot be postponed.

In practice, there are cohort temporary authorisations for use (ATUc) and nominative temporary authorisations for use (ATUn). Nominative ATUs are issued for a single named person who cannot participate in a clinical trial, at the request and under the responsibility of the prescribing physician where the medicinal product has an efficacy/safety ratio presumed to be favourable for the patient based on available data.

Cohort ATUs can be issued for medicinal products whose efficacy and safety are strongly presumed, for a group of patients treated and monitored in accordance with criteria defined in a protocol for therapeutic use and collection of information (PTU). They are issued at the request of the holder of the distributing rights who has filed or is in the process of filing a MA request within a set timescale.

In France, exceptionally and by derogation, it is therefore possible to have access to a medicinal product under development (Fig. 1) [21]. More and more ATUc are being issued in parallel with the processing of the MA request. The ANSM expects to handle more than 22 ATUc in 2018. The timeframe for assessing and deciding whether an ATUc should be granted is less than 6 months (Table 2) [11].

Recently, in September 2018, the ANSM took a new initiative and published guidelines on ATUc on its website as part of its modernization and transparency programme. The guidelines are accessible to health professionals via a portal and aim to simplify application procedures for ATUs and exchanges between prescribing physicians and the Agency [22].

Currently, the ATU process can only be used for a medicinal product’s first indication. However, a given medicinal product can be developed and provide a benefit to patients in several indications. Therefore, a further indication may completely correspond to the requirements of an ATU. Currently, Temporary use recommendations (RTU) could provide an answer to the problem but they are not much used and do not seem to meet the needs of practitioners. Temporary Use Recommendations are used above all to regulate...
Table 2  Review of nominative and cohort temporary authorisation for use (temporary authorisation for use, ATUs) in France from 2013 to 2017 [11].

<table>
<thead>
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<th>2013</th>
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<th>2017</th>
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<tbody>
<tr>
<td>Nominative ATUs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of ATU granted</td>
<td>27,550</td>
<td>25,521</td>
<td>24,791</td>
<td>27,095</td>
<td>22,295</td>
</tr>
<tr>
<td>Medicinal products made available per year</td>
<td>241</td>
<td>208</td>
<td>219</td>
<td>205</td>
<td>253</td>
</tr>
<tr>
<td>Patients included</td>
<td>19,982 Including 12,713 in whom treatment was initiated</td>
<td>18,831 Including 12,822 in whom treatment was initiated</td>
<td>17,829 Including 12,175 in whom treatment was initiated</td>
<td>19,625 Including 14,029 in whom treatment was initiated</td>
<td>16,621 Including 11,390 in whom treatment was initiated</td>
</tr>
</tbody>
</table>

The number of patients treated in the framework of an ATUc was 8250

| Cohort ATUs |               |               |               |               |               |
| Number of ATUc granted | 9             | 33a           | 22            | 23a           | 13            |
| Medicinal with a cohort ATU having been granted MA | 7             | 26a           | 25            | 25a           | 13            |
| Patients included | 6136          | 12,111        | 10,216        | 11,909        | 8250          |

Courtesy Agence nationale de sécurité du médicament et des produits de santé (ANSM).
a Number of products specialities.

prescriptions that do not comply with the marketing authorisation (provided there is a therapeutic need and the B/R ratio of the medicinal product is presumed to be favourable). The problem therefore lies in making medicinal product indication extensions (e.g. anti-PD-1 immunotherapies) eligible for the ATU process if they meet the aforementioned requirements. The proposal would make it possible, as with first-time registrations, to make products with still long assessment periods available at an early stage. It is also one of the CSIS 2018 measures and one of the articles of the social security financing bill (PLFSS) 2019 (Article 42) [23].

Proposal 5: Implement the CSIS measure concerning the extension of the ATU process to indication extensions if the extension in question corresponds to the ATU eligibility criteria, while ensuring financing procedures are simplified so it can be applied concretely.

The timeframes for examining ATUc applications are variable today and need to be optimized, particularly with a view to the granting of indication extension ATUs (ATUex).

Given that ATUs grant early access to medicinal products, it is essential that patients, clinicians and the community be informed about the possibility that the ATU may be withdrawn and the medicinal product become unavailable if it is formally established that the B/R ratio of the early-accessed medicinal product has is unfavourable.

Proposal 6: Implement an assessment and decision period of 90 days at the most with a “fast track” option for indication extensions eligible for ATUex. Anticipate ATUs for indication extensions by the licence holder sending an ATUex letter of intent including the schedule of planned submissions to the ANSM.

Proposal 7: Inform practitioners and patients that in terms of provision and financing, the measure is exceptional and may be temporary, subject to reassessment for consolidation or withdrawal.

Finally, as it is a common approach (industrialists/health agencies) to support access to innovation, it seems essential that industrialists make it easier to gain access to innovative products by promoting programmes such as “early access programmes” (EAP) like in other countries. This process is not used much in France and could be useful to ensure treatment continuity for patients who have already started using an innovative treatment.

Proposal 8: Ensure continuity of treatment for patients awaiting treatment (for example at the end of a clinical trial) by defining a regulatory framework for the establishment of simple and practical EAPs.
Financing of medicinal products in an early access context

Regarding current financing of medicinal products that are accessible through early access programmes (MA following an ATU), the issues identified centre around three major themes:

• the HAS assessment and CEPS negotiation procedures and deadlines;
• patient access (AB), pricing (in relation to the improvement in actual benefit or IAB) and post-registration follow-up (real-life data);
• the financing of IAB IV medicinal products available only in hospitals and their real accessibility for the patient;
• the price of medicinal products with ATUs.

Assessment by the HAS

In order to promote early access, the HAS has implemented various actions as follows:

• a fast track procedure with the possibility of making a submission before the Committee for medicinal products for human use (CHMP) issues a positive opinion when the medicinal product is presumed to be innovative;
• a fast track procedure with the possibility of making a submission after the CHMP has issued a positive opinion for all medicinal products ("pre-submission" procedure);
• prioritization of programming with medicinal products with an ATU programmed first.

A study was conducted by the HAS to quantify these delays for medicinal products having benefited from ATUs. Between January 1, 2016 and May 31, 2018 (2.5 years), the HAS assessed 141 new medicinal products for which a first-registration application was submitted to the TC and which were examined through a complete procedure (PIC) [21]. Of these 141 medicinal products, 40 were granted ATUs (including 18 with orphan drug status) (Fig. 2).

Concerning dossier examination times, the dossiers were transmitted to the CEPS on average 136 days (median 126 days) after the administrative validation for the medicinal products having been granted an ATU and 142 days (median 130 days) for medicinal products without an ATU. The dossier assessment period mainly consisted of the time it took to process the dossier (that is to say between the administrative validation of the dossier and its examination by the Commission) and the period between its examination and the hearing of the industrialist when a hearing had been requested. Sixty per cent (24/40) of medicinal products having been granted an ATU were the subject of a hearing versus only 10% of those without an ATU.

In view of the forthcoming granting of ATUs for indication extensions, the examination times for these new ATUs need to be optimized.

There is a lag of 1 to 2 months between the TC opinion and the CEESP opinion. In 2017, for the 23 products eligible for a medical-economical assessment, 8/23 opinions have been published to date.

In a logic of global coordination of early access, it would be desirable for the various HAS Committees to assess dossiers in a synchronized manner without causing delays. Concomitance can be achieved only by settling on the shortest timeframes. For this, it is important for all players to act responsibly, including industrialists who should not abuse of requests to suspend medical-economical assessments following technical exchanges with the HAS. Early meetings with the HAS theoretically help to avoid these pitfalls and anticipate the expectations of the CEESP.

Proposal 10: Ensure the different committees of the HAS systematically assess cases concomitantly so their opinions are synchronized.

![Figure 2. Distribution of medicinal products assessed with a full procedure and having or not having been granted an authorisation temporaire d’utilisation (temporary authorisation for use, ATU) between January 1, 2016 and May 31, 2018. The x-axis shows the year and the y-axis the number of medicinal products [21]. Courtesy Agence nationale de sécurité du médicament et des produits de santé (ANSM).](image)

Proposal 9: Free-up resources at the HAS to refocus its assessment activity on priority cases by replacing, for example, registration renewals (systematic reassessment of each proprietary medicinal product every 5 years) by a program of selected reassessments that are clinically and/or economically justified.

2 For the published CEESP opinions for 2016-2018: in 12/24 cases the CEESP opinion was given after the TC opinion (average time = 60 days) and in 12/24 cases the CEESP opinion was given prior to the TC opinion (average time = 38 days).
In addition, 65% (26/40) of the medicinal products that were granted an ATU were assessed with the help of external specialists of the disease with no conflicts of interest and 41% (9/22) were assessed with the help of a patient organisation. The difficulty of identifying competent experts with no conflicts of interest for the assessment of the dossiers may have contributed to the lengthening of the deadlines (many experts do not meet these two requirements in certain disciplines). Innovations are required in terms of expertise and new models need to be proposed favouring bottom-up expertise that will generate patient care leaders (PCL) in contrast to key opinion leaders (KOL) whose conflicts of interest make any solicitation unacceptable. The institutions emphasized the relevance of having a pool of experts without any conflicts of interest who could be involved in the assessment decisions, thereby reducing delays. Other authors have pointed out that it is possible, in certain cases, to call on experts whose conflicts of interests have been disclosed (for rare diseases in particular) so they may participate in assessments in an advisory capacity. This is provided for in the expertise charter for rare diseases when it is not possible to call on competent experts without conflicts of interest.

Proposal 11: Implementation of CSIS measure No. 2.1.c by establishing an agreement between health agencies and health care institutions to constitute a pool of health experts with an advisory role. Reinforce the attractiveness of providing expertise by rewarding expertise in academic careers and more broadly, in professional careers.

Regarding the use of Fast Track procedures at the HAS, less than 15% of the pharmaceutical companies with medicinal products having been granted an ATU have used them. No difference was observed between medicinal products that had been granted an ATU and those that had not (12% vs. 15%, respectively). These results underline the under-utilization of the accelerated procedures available to industrialists, despite their established and effective implementation, and communication of the TC on this subject.

Proposal 12: Encourage industrialists to use the procedures available to them for faster assessments.

Price negotiations with the CEPS

The LEEM monitored delays [24] for oncology drugs that had been granted an ATU and for which registration was being requested for the first time and had obtained a TC opinion between May 2015 and December 2017 and found that the duration of the price negotiations exceeded the regulatory 180 days. At the July 2018 CSIS, the CEPS and industrialists committed to better defining the framework and transparency of the negotiations.

Proposal 13: Apply CSIS flagship measure No.2 by implementing the following 5 actions:
- systematically update the economic interest notifications sent by companies to the CEPS within two weeks of the Transparency Committee’s final opinion;
- respect a period of one month at the most between receipt of the price dossier and the first price counter-proposal of the CEPS to accelerate the negotiation process;
- introduce an obligation to justify the proposals of the CEPS and the industrialists based on the regulatory and contractual principles in force as well as the methodological elements taken into account for the construction of price proposals;
- transform the IAB V Fast-Track experimentation referred to in Article 24 of the previous framework agreement into a durable arrangement;
- define a contractual file closure procedure in the absence of agreement.

Finally, presupposed innovative medicinal products must be made more visible to adapt responses to priorities at an early stage.

Proposal 14: Improve prospection of high-potential medicinal products by implementing CSIS 2018 measure No. 2.4: implementation of “Horizon Scanning” in 3 stages:
- create an observatory for the identification of expected technologies and innovations;
- pool impact assessments from this observatory to detect future developments;
- create a database using existing tools to collect this data.

Patient access (AB), pricing (IAB), and post-registration follow-up

Assessment by the TC (determination of the actual clinical benefit or AB and improvement in actual benefit or IAB)

While ATUs and the MAs are granted on the basis of an intrinsic B/R ratio that is presumed to be favourable, the actual benefit and improvement in actual benefit of medicinal products are assessed in comparison to available treatments to determine whether they should be reimbursed and to set a price. The assessment concerns whether treatment-related costs should be born National health insurance by comparison with existing treatments and is not an isolated analysis of the B/R ratio.

The study conducted by the HAS on medicinal products that were granted an ATU [21] found that of the 49

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1 Patient organisations have been able to contribute to assessments from November 2016, explaining the change of scope.
indications/secondary indications identified for the 40 medicinal products, the actual clinical benefit was considered sufficient in 84% of the cases and insufficient in 16% of the cases (8/49) to justify financing by National Health Insurance. Of the 40 medicinal products that were granted an ATU, actual clinical benefit was considered insufficient for all the indication(s) in 5% of cases (2/40) and the medicinal products were not marketed in France. The figure was 10% (10/101) for medicinal products that did not have an ATU.

Regarding the indications of the medicinal products that were granted an ATU and whose improvement in actual benefit was assessed (n = 41), the improvement in actual benefit was III (IAB III) in 12% of the cases (5/41), IV (IAB IV) in 37% of the cases (15/41) and V (IAB V) in 51% of the cases (21/41) [21]. It should be stressed that there is no direct link between the granting of an ATU and the attribution of an IAB score, firstly because ATUs are often granted in different, more restricted indications than the ones in which improvement in actual benefit is assessed, and secondly because the granting of an ATU attests to the fact that a medical need exists. While a medical need may be taken into account by the TC to underscore a level of evidence, the amount of effect or the clinical relevance of a gain, it cannot directly impact the IAB score alone. The uncertainty and preliminary nature of the data submitted to the TC for these early access products can lead to their improvement in actual benefit being considered minor or lacking due to insufficient data. This proves that it would be fitting to expand on the idea of temporary reimbursement subject to reassessment and collection of real-life data.

**Proposition 15:** Capitalize on the French real-life data collected in the framework of ATUs and post-ATUs (efficacy, care pathway, safety, organizational impact.) by making the prescription and reimbursement of medicinal products having been granted ATUs conditional on data collection by the prescriber, which should be mandatory.

Furthermore, medical and administrative databases could be enriched (matching, interoperability) and thus become sources of data that could be used for the constitution of dossiers for the HAS.

**Proposal 16:** Make the generation of this data more a part of the reimbursement examination process through more systematic use of databases and the medicalisation of the national health insurance inter-regime information system (SNIRAM).

To ensure that patients gain access to presumably "high potential" medicinal products in a context of a serious disease and unmet medical need, they could be offered temporary treatment which could be renewed subject to data being collected, bearing in mind that the treatment should not be proposed if there are any doubts about its safety and efficacy for the patients.

**Proposal 17:** Eligibility criteria for conditional reimbursement could thus be defined in situations where a lack of financing in the light of preliminary data could lead to a loss of opportunity for patients (critical illness with an unmet medical need) where, of course, initial data show that the medicinal product could be of clinical value and it will be possible to generate future data to remove initial uncertainties. Temporary reimbursement would need to be conditional on the collection of "real life evidence" to eliminate short-term uncertainties in a re-assessment within 5 years (this proposal is included in the TC set of guidelines published on 15 October 2018 on the HAS website).

**Post-registration follow-up**

Preliminary data submitted to the HAS for early-access medicinal products frequently leads to requests from the HAS to complete the data with additional studies.

The study conducted by the HAS determined that for 40% (16/40) of the medicinal products with an ATU, the TC requested additional data (generated by the Post-Registration Studies and/or the collection of follow-up data). In addition, over the 2.5-year study period, 15% (6/40) of the medicinal products granted an ATU had been re-assessed following their initial assessment [21].

The possibility of re-assessing medicinal products made available at an early stage after a specified period would guarantee the quality of the data collected and enhance the value of ATU and post-ATU data (which can represent more than 1 year of real-life follow-up).

**Proposal 18:** Develop a strategy around the use of real-life data and set up an appropriate governing structure for the assessment and use of these data. Propose a re-assessment of the product within 5 years with new data.

Finally, the centralization of existing databases in France with the creation of a "health data hub" should facilitate the use of data, particularly in order to document the real-life use of health products.

**Proposal 19:** Apply CSIS flagship measure No. 9: structure the health data ecosystem in France by creating a "health data hub".

**Financing**

While the expansion of ATUs to line extensions is intended to enhance early access, the administrative complexity of their financing should not hinder pharmaceutical companies from submitting ATU applications. A price identical to indication 1 could be proposed, but may seem unrealistic if the target population of indication 2 is much larger than that of indication 1.
Furthermore, some expensive medicinal products that are given an improvement in actual benefit of IV (IAB IV) are then not included on the list of medicinal products billable over and above inpatient services as they do not meeting the eligibility criteria (IAB ≤ III in particular). Currently, the criteria (cumulative) are as follows:
• actual benefit (AB) considered significant;
• attribution of:
  o an IAB I, II or III,
  o or an IAB IV or V, with identification of a comparator included on the list of medicinal products billable over and above inpatient services,
  o or an IAB IV with no alternative treatment and recognition of a value for public health (ISP);
• Use of the product mainly in hospitals and incompatibility of the price of the product with the prices of hospital stays.

Thus, a product having been attributed an added clinical value of IV (IAB IV) which is of no value for public health and does not have a comparator on the list of medicinal products billable over and above inpatient services will not be able to be financed over and above the diagnosis-related group-based fee.

Proposal 21: Open the list of medicinal products billable over and above inpatient services to IAB IV products, with the prices being set in the context of conventional discussions with the CEPS pending a reform of the assessment or financing procedures, and integrate temporary reimbursements with an appropriate pricing mechanism.

## Conclusion

The first, very encouraging finding is the increase in the number of innovations that will potentially become part of the early access programmes for patients with serious diseases the treatment of which should improve.

France’s involvement in early access to new molecules is well recognized: in 2016, it was the European country where the most clinical trials were conducted [25]. The rapid setting up of Phase I and I/II trials in our country must remain a priority. The ATU system, a unique access model, gives patients rapid access to medicinal products with high-potential as long as they are presumed to be effective and safe for the patient. Identification and access to these high-potential medicinal products is possible thanks to the expertise and competence of our regulatory and assessment agencies.

However, while early access mechanisms are well established in France, a lack of clearness and predictability of some of them can at times lead to access to the products being substantially delayed. The potential uncertainty generated by incomplete data may hinder the “risk-taking” of authorities as regards the granting of early access and the financing of products presumed to be promising based on preliminary data.

The 21 proposals in this article aim to improve the situation in the short to medium term by creating smooth, interruption-free access to treatments for patients between the clinical trial and marketing period. Some of the proposals concern the prioritization, coherence and use of the procedures already in place to improve the inclusion of different players and exchanges between them, as well as to optimize deadlines (proposals 3, 6, 7, 8, 9, 10, 11, 12, 13). Furthermore, successful experiences and well-established modalities should motivate the expansion of existing mechanisms to other players or products (Proposals 1, 2, 4, 5, 14, 17, 19) on condition, however, that well defined and clear financial support is provided (proposals 9, 20, 21). Finally, the generation of data must be made an integral part of all early access mechanisms and must be developed as soon as the product is made available by encouraging the use of the French databases (proposals 15, 16, 17, 18, 19). Currently, data collection that would help to confirm whether a product is effective (or not) in real-life situations is insufficiently used.

Implementation of our proposals could help with the necessary adaptation of access mechanisms so the challenges posed by future innovations may be anticipated. Ensuring continued product availability while responding to the uncertainty generated by preliminary data will enable the establishment of new access and conditional financing mechanisms. The reversibility of the mechanisms will enable risks to be managed appropriately, while giving patients and doctors the option of using to high-potential molecules at an early stage.

## Acknowledgments

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## Disclosure of interest

N.A: employee of the French national agency for medicines and health products safety.
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M.G: employee of the French national authority for health. Close relatives employed by SANDOZ Pharma, Générale de santé and CHUGAI Pharma.
C.K: employee of Takeda France.
L.B: employee of the French national agency for medicines and health products safety.
A.-C.R: employee of AstraZeneca France.
N.H.-L: head of AcSé programme at the National cancer institute.
F.M: employee of the Leem.
F.G: the author declares that she has no conflicts of interest.
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F.L: employee of Janssen France.
B.P.-L: employee of Sanofi France.
T.C: employee and shareholder of Amgen France.
C.L.J: employee of the public hospitals of Paris (AP-HP) and Paris Diderot university. Participates in clinical trials as an investigator and participates in committees and meetings for Novartis, Roche, AstraZeneca, Lilly and IQVIA.
J.-F.B: employee of the public hospitals of Paris (AP-HP) and Paris Diderot university. Participates in clinical trials as an investigator and participates in committees and meetings for Novartis, Roche, AstraZeneca, Lilly, IQVIA, Sanofi, Takeda, Bayer, GlaxoSmithKline, Janssen, Pfizer.
B.M: employee of Roche France.

### Appendix 1. Criticality grid for the assessment of clinical trial authorisation dossiers

Documents to consult: European form "Clinical Trial Application Form"; National form "Letter requesting authorisation to conduct research in human beings mentioned in section 1 of article L.1121-1 of the code of public health relating to medicinal products". Eligible for level 2 pharmacovigilance prioritization.

<table>
<thead>
<tr>
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<th>Criticality C</th>
<th>Utility U</th>
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<td></td>
</tr>
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<tr>
<td>Phase III</td>
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<tr>
<td>Complex design (multiphase, several products, combinations)</td>
<td>C4*</td>
<td>U2</td>
<td></td>
</tr>
<tr>
<td>Targeted therapy/companion study</td>
<td>C4</td>
<td>U2</td>
<td></td>
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<tr>
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<td></td>
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<tr>
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<td>Experimental products</td>
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**Criticality**

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<th>Utility U</th>
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<tr>
<td>C4</td>
<td>Type of dossier</td>
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**Pharmacovigilance risk level**

1: assessment of FNs, SUSARs and DSURs; 2: assessment of FNs, SUSARs deaths/life-threatening events/DME list and DSURs; 3: assessment of FNs, SUSARs deaths/life-threatening events.

<table>
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<tr>
<td>U2</td>
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**Assessment**

- No 59
- Quality
- Non clinical
- Full clinical (C1—C4)
- Securing clinical use (C—C2)
- Clinical loss of opportunity (C3)

DSMB: data safety monitoring board; DSUR: drug safety update report; FR: France; PIP: plan d’investigation pédiatrique (pediatric investigational plan); MA: marketing authorization; SUSAR: suspected unexpected adverse reaction.

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